ORIGINAL ARTICLE

# Riociguat for the Treatment of Chronic Thromboembolic Pulmonary Hypertension

Hossein-Ardeschir Ghofrani, M.D., Andrea M. D'Armini, M.D., Friedrich Grimminger, M.D., Marius M. Hoeper, M.D., Pavel Jansa, M.D., Nick H. Kim, M.D., Eckhard Mayer, M.D., Gerald Simonneau, M.D., Martin R. Wilkins, M.D., Arno Fritsch, Ph.D., Dieter Neuser, M.D., Gerrit Weimann, M.D., and Chen Wang, M.D., for the CHEST-1 Study Group*

## ABSTRACT

### BACKGROUND

Riociguat, a member of a new class of compounds (soluble guanylate cyclase stimulators), has been shown in previous clinical studies to be beneficial in the treatment of chronic thromboembolic pulmonary hypertension.

### METHODS

In this phase 3, multicenter, randomized, double-blind, placebo-controlled study, we randomly assigned 261 patients with inoperable chronic thromboembolic pulmonary hypertension or persistent or recurrent pulmonary hypertension after pulmonary endarterectomy to receive placebo or riociguat. The primary end point was the change from baseline to the end of week 16 in the distance walked in 6 minutes. Secondary end points included changes from baseline in pulmonary vascular resistance, N-terminal pro–brain natriuretic peptide (NT-proBNP) level, World Health Organization (WHO) functional class, time to clinical worsening, Borg dyspnea score, quality-of-life variables, and safety.

### RESULTS

By week 16, the 6-minute walk distance had increased by a mean of 39 m in the riociguat group, as compared with a mean decrease of 6 m in the placebo group (least-squares mean difference, 46 m; 95% confidence interval [CI], 25 to 67; P<0.001). Pulmonary vascular resistance decreased by 226 dyn · sec · cm$^{-5}$ in the riociguat group and increased by 23 dyn · sec · cm$^{-5}$ in the placebo group (least-squares mean difference, –246 dyn · sec · cm$^{-5}$; 95% CI, –303 to –190; P<0.001). Riociguat was also associated with significant improvements in the NT-proBNP level (P<0.001) and WHO functional class (P=0.003). The most common serious adverse events were right ventricular failure (in 3% of patients in each group) and syncope (in 2% of the riociguat group and in 3% of the placebo group).

### CONCLUSIONS

Riociguat significantly improved exercise capacity and pulmonary vascular resistance in patients with chronic thromboembolic pulmonary hypertension. (Funded by Bayer HealthCare; CHEST-1 and CHEST-2 ClinicalTrials.gov numbers, NCT00855465 and NCT00910429, respectively.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Ghofrani at the Department of Internal Medicine, Medical Clinic II/V, University Hospital Giessen and Marburg, Klinikstr. 33, Giessen 35392, Germany, or at ardeschir.ghofrani@innere.med.uni-giessen.de.

*The full list of investigators and trial committees of the Chronic Thromboembolic Pulmonary Hypertension Soluble Guanylate Cyclase–Stimulator Trial 1 (CHEST-1) is provided in the Supplementary Appendix, available at NEJM.org.

N Engl J Med 2013;369:319-29.
DOI: 10.1056/NEJMoa1209657

Chronic thromboembolic pulmonary hypertension is characterized by obstruction of the pulmonary vasculature by residual organized thrombi,[1] leading to increased pulmonary vascular resistance, progressive pulmonary hypertension, and right ventricular failure.[2,3] Patients with chronic thromboembolic pulmonary hypertension have a poor prognosis unless they receive treatment early.[4]

Pulmonary endarterectomy is the standard treatment for chronic thromboembolic pulmonary hypertension and is the only potentially curative treatment.[5] However, surgery is not an option for all patients; some patients are ineligible for surgery owing to the occlusion of distal vessels or coexisting conditions, some decline surgery, and some do not have access to expert surgical centers.[5-8] Operability should be assessed with the use of high-quality imaging, with each patient undergoing review at an experienced pulmonary-endarterectomy center.[6,7] Furthermore, some patients who undergo pulmonary endarterectomy have persistent or recurrent pulmonary hypertension after surgery. To date, pharmacologic therapies have been approved for pulmonary arterial hypertension (group 1 in the Dana Point classification[1]) but not for chronic thromboembolic pulmonary hypertension (Dana Point group 4), highlighting a substantial unmet need.[9]

Riociguat is a member of a new class of therapeutic agents called soluble guanylate cyclase stimulators.[10] Impairment of nitric oxide synthesis and signaling through the nitric oxide–soluble guanylate cyclase–cyclic guanosine monophosphate pathway is involved in the pathogenesis of pulmonary hypertension.[11,12] Riociguat has a dual mode of action, directly stimulating soluble guanylate cyclase independently of nitric oxide, and increasing the sensitivity of soluble guanylate cyclase to nitric oxide.[10,11] Riociguat increases the level of cyclic guanosine monophosphate, resulting in vasorelaxation and antiproliferative and antifibrotic effects, as shown in experimental models of pulmonary hypertension.[13,14]

In previous clinical studies involving patients with pulmonary arterial hypertension or chronic thromboembolic pulmonary hypertension, riociguat significantly increased exercise capacity and improved hemodynamic variables.[10,15] Here we present the results of the Chronic Thromboembolic Pulmonary Hypertension Soluble Guanylate Cyclase–Stimulator Trial 1 (CHEST-1), a phase 3 study investigating the efficacy and side-effect profile of riociguat in patients with chronic thromboembolic pulmonary hypertension who were considered by experienced surgeons to be ineligible for surgery or who had persistent or recurrent pulmonary hypertension after pulmonary endarterectomy.

## METHODS

### STUDY DESIGN AND OVERSIGHT

We conducted this 16-week, double-blind, randomized, placebo-controlled study at 89 centers in 26 countries. The study was designed by the first author and the steering committee (see the Supplementary Appendix, available with the full text of this article at NEJM.org) in collaboration with the sponsor, Bayer HealthCare. The institutional review board at each participating center approved the protocol. Data were collected according to Good Clinical Practice guidelines at the investigation sites. The steering committee had access to the complete database. The statistical analysis was performed by a statistician employed by the sponsor and was reviewed by the first author. The manuscript was prepared by the first author, and editorial assistance, funded by the sponsor, was provided by Adelphi Communications. The first author, with approval from the coauthors, made the decision to submit the manuscript for publication. The academic authors assume full responsibility for the accuracy and completeness of the data and all the analyses, as well as for the fidelity of this report to the trial protocol, which is available at NEJM.org.

### SELECTION OF PATIENTS

Patients 18 to 80 years of age were included if they had chronic thromboembolic pulmonary hypertension that was adjudicated to be technically inoperable or if they had persistent or recurrent pulmonary hypertension after undergoing pulmonary endarterectomy. Additional inclusion criteria were a 6-minute walk distance of 150 to 450 m, pulmonary vascular resistance of more than 300 dyn · sec · $cm^{-5}$, and a mean pulmonary-artery pressure of at least 25 mm Hg. Chronic thromboembolic pulmonary hypertension was diagnosed with the use of two or more of the following imaging methods: ventilation–perfusion scanning, pulmonary angiography, spiral computed tomography, or magnetic resonance angiography.

Patients were excluded if they had received an endothelin-receptor antagonist, prostacyclin analogue, phosphodiesterase type 5 inhibitor, or nitric oxide donor within the 3 months before study entry. Written informed consent was obtained from all the patients.

### STUDY PROCEDURES

Patients who were considered to be potentially eligible for trial participation after the initial screening were entered into a pretreatment phase to permit a systematic assessment of operability and a detailed evaluation of all other enrollment criteria. The criteria for inoperability and the specifics of their adjudication are provided in the Supplementary Appendix.

After the completion of the pretreatment phase, eligible patients were randomly assigned in a 1:2 ratio to receive placebo or riociguat. The dose-adjustment plan for riociguat is described in detail in Figure S1 in the Supplementary Appendix. Briefly, riociguat was adjusted from a starting dose of 1 mg three times daily according to systolic systemic arterial pressure and signs or symptoms of hypotension (final range, 0.5 mg to 2.5 mg three times daily). The doses reached at the end of the 8-week adjustment phase were considered to be the appropriate dose for the patient, and the patient continued taking the drug at that dose for another 8 weeks.

Patients were seen at weeks 2, 4, 6, and 8 (during the dose-adjustment phase) and then at weeks 12 and 16 (during the maintenance phase). At each visit, clinical assessments and blood tests were performed. Patients who discontinued therapy for any reason were withdrawn from the trial; these patients underwent an efficacy assessment at the termination visit and had no further efficacy assessments after withdrawal. All surviving patients returned for a follow-up assessment of safety at 30 days. Patients completing the 16-week study were eligible to participate in a long-term, open-label extension study (CHEST-2).

### OUTCOME MEASURES

The primary end point was the change from baseline to the end of week 16 in the distance walked in 6 minutes. Secondary efficacy end points included changes from baseline to the end of week 16 in pulmonary vascular resistance, N-terminal pro–brain natriuretic peptide (NT-proBNP) level, World Health Organization (WHO) functional class (an adaptation of the New York Heart Association functional classification), time to clinical worsening (as defined in the Supplementary Appendix), Borg dyspnea score (which ranges from 0 to 10, with 0 representing no dyspnea and 10 maximal dyspnea), the score on the EuroQol Group 5-Dimension Self-Report Questionnaire (EQ-5D; in which scores range from –0.6 to 1.0, with higher scores indicating a better quality of life), and the score on the Living with Pulmonary Hypertension (LPH) questionnaire (an adaptation of the Minnesota Living with Heart Failure Questionnaire, with scores ranging from 0 to 105 and higher scores indicating a worse quality of life). Adverse events and laboratory variables were assessed throughout the study and during the safety follow-up period.

### STATISTICAL ANALYSIS

For the study to detect a least-squares mean difference from baseline of 30 m in the 6-minute walk distance with riociguat, at a power of 90% and a two-sided significance level of 5%, we calculated that we would need to enroll 174 patients in the riociguat group and 87 in the placebo group. The primary efficacy analysis was performed with data from the modified intention-to-treat population (all patients who underwent randomization and received at least one dose of the study medication). A per-protocol analysis was also performed (see the Supplementary Appendix). Missing values due to patient withdrawal or death were imputed as described in the Supplementary Appendix.

For evaluation of the primary end point, a two-sided test at the 5% significance level for the difference in the treatment effect between the riociguat group and the placebo group was performed. The comparison was carried out with the use of analysis of covariance, with baseline value as a covariate and treatment group and region as main effects. This was followed by a test of normality of the residuals (Shapiro–Wilk test), and on rejection, a nonparametric stratified Wilcoxon test was used to assess the change from baseline in the 6-minute walk distance.

The secondary efficacy variables were formally tested if the primary comparison was significant at a two-sided level of 5%. A hierarchical testing procedure was performed, with the variables in the following order: pulmonary vascular resistance, NT-proBNP level, WHO func-

tional class, time to clinical worsening, Borg dyspnea score, EQ-5D score, and LPH questionnaire score (see the Supplementary Appendix). The changes in the variables for the secondary efficacy end point that were measured on a semicontinuous scale were analyzed with the use of the same methods as those for the 6-minute walk distance. Changes in WHO functional class and Borg dyspnea score were analyzed with the use of the stratified Wilcoxon test. Time to clinical worsening was analyzed with the use of a stratified log-rank test, and safety was analyzed descriptively. Adverse events during the study period included all adverse events that started or worsened from the time of administration of the first dose of the study drug until 2 days after the administration of the last dose.

## RESULTS

### PATIENTS

From February 2009 through February 2012, a total of 261 patients underwent randomization and received at least one dose of study medication (173 patients in the riociguat group and 88 in the placebo group) (Fig. 1). The characteristics of the patients at baseline were well balanced between the two groups (Table 1). Most patients

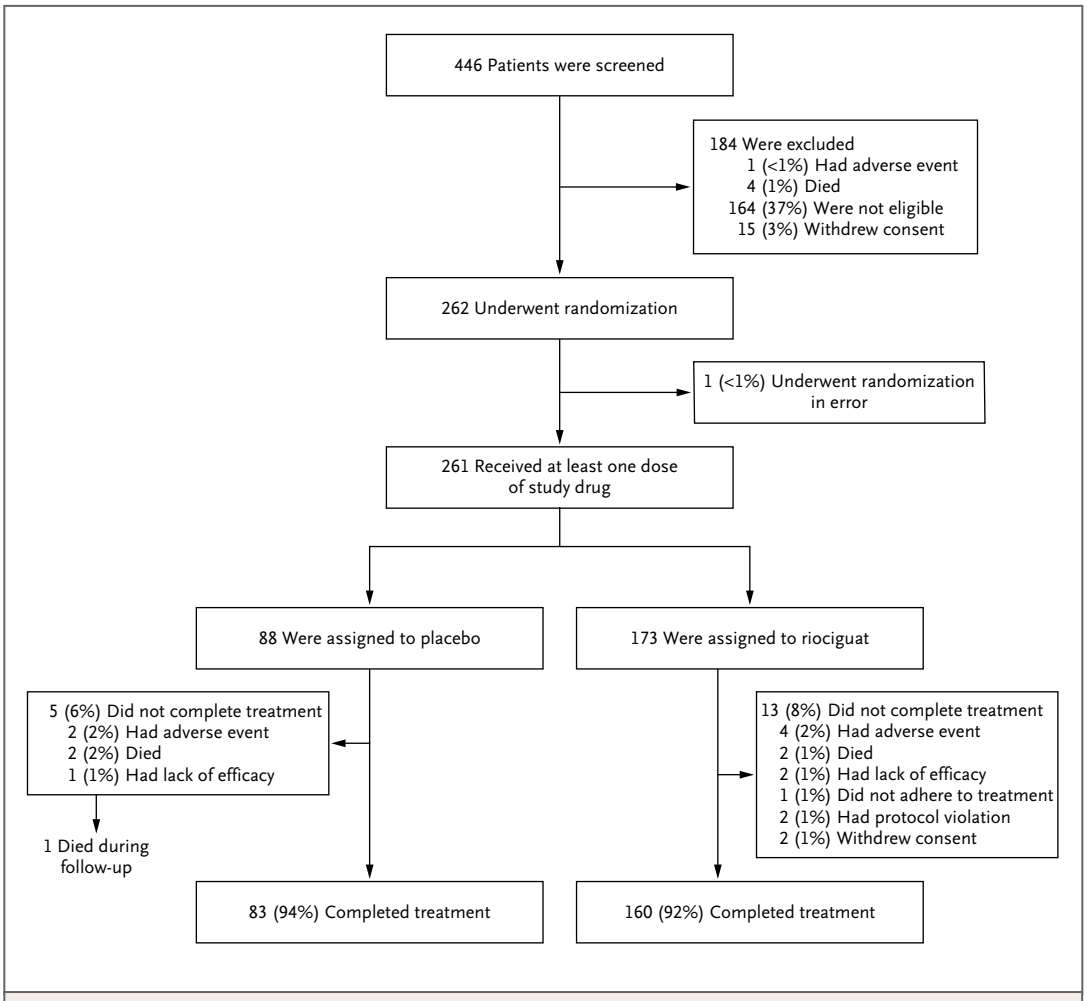


**Figure 1. Screening, Randomization, and Follow-up.**

The one patient who underwent randomization in error was ineligible for the study; this patient was assigned to but not treated in the riociguat group. Of the five patients who did not complete treatment, one patient in the placebo group who withdrew owing to an adverse event died during the 30-day follow-up period.

**Table 1. Baseline Demographic and Clinical Characteristics of the Patients.***

| Characteristic | Placebo (N=88) | Riociguat (N=173) | Total (N=261) |
|---|---|---|---|
| Female sex — no. (%) | 54 (61) | 118 (68) | 172 (66) |
| Race — no. (%)† | | | |
| White | 65 (74) | 120 (69) | 185 (71) |
| Black | 1 (1) | 7 (4) | 8 (3) |
| Asian | 20 (23) | 37 (21) | 57 (22) |
| Not reported | 2 (2) | 8 (5) | 10 (4) |
| Mixed | 0 | 1 (1) | 1 (<1) |
| Age — yr | 59±13 | 59±14 | 59±14 |
| Body-mass index‡ | 28±5 | 27±6 | 27±6 |
| Chronic thromboembolic pulmonary hypertension — no. (%) | | | |
| Inoperable | 68 (77) | 121 (70) | 189 (72) |
| Postoperative | 20 (23) | 52 (30) | 72 (28) |
| WHO functional class — no. (%)§ | | | |
| I | 0 | 3 (2) | 3 (1) |
| II | 25 (28) | 55 (32) | 80 (31) |
| III | 60 (68) | 107 (62) | 167 (64) |
| IV | 2 (2) | 8 (5) | 10 (4) |
| Data missing | 1 (1) | 0 | 1 (<1) |
| 6-Min walk distance — m | 356±75 | 342±82 | 347±80 |

* Plus–minus values are means ±SD. There were no significant differences in baseline characteristics between the riociguat and placebo groups.
† Race was determined by the investigator.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ The World Health Organization (WHO) functional class ranges from I to IV, with higher numbers indicating greater functional limitations.

were in WHO functional class II or III, and more patients were classified as having inoperable chronic thromboembolic pulmonary hypertension (72% of all patients) than postoperative persistent or recurrent pulmonary hypertension (28%). A total of 18 patients withdrew from the study before week 16 (Fig. 1).

### DOSING

At week 16, a total of 77% of patients who were still participating in the study were taking the maximal riociguat dose of 2.5 mg three times daily, with 12%, 6%, 4%, and 1% taking riociguat at doses of 2.0 mg, 1.5 mg, 1.0 mg, and 0.5 mg three times daily, respectively. During the study, the dose of the study drug was decreased in 18 patients (10%) in the riociguat group, as compared with 3 (3%) in the placebo group.

### PRIMARY END POINT

At week 16, the 6-minute walk distance had increased from baseline by a mean of 39 m in the riociguat group, as compared with a mean decrease of 6 m in the placebo group (least-squares mean difference, 46 m; 95% confidence interval [CI], 25 to 67; P<0.001), on the basis of an analysis of the modified intention-to-treat population with missing values imputed (Table 2 and Fig. 2). In sensitivity analyses for missing data that used statistical methods for longitudinal data (see the Supplementary Appendix), the benefit of riociguat was similar to that observed in the main analysis (Table S1 in the Supplementary Appendix). The increase in the 6-minute walk distance in the per-protocol population (Table S2 in the Supplementary Appendix) was consistent with the increase in the main analysis. The treatment

**Table 2. Change from Baseline to End of Week 16 in Primary and Secondary End Points and in Hemodynamic Variables.***

| End Point | Placebo | | | Riociguat | | | Least-Squares Mean Difference (95% CI) | P Value† |
|---|---|---|---|---|---|---|---|---|
| | No. of Patients | Baseline | Change | No. of Patients | Baseline | Change | | |
| **Primary end point** | | | | | | | | |
| 6-Min walk distance (m)‡ | 88 | 356±75 | −6±84 | 173 | 342±82 | 39±79 | 46 (25 to 67) | <0.001 |
| **Secondary end points** | | | | | | | | |
| Pulmonary vascular resistance (dyn·sec·cm$^{-5}$) | 82 | 779±401 | 23±274 | 151 | 791±432 | −226±248 | −246 (−303 to −190) | <0.001 |
| NT-proBNP (pg/ml) | 73 | 1706±2567 | 76±1447 | 150 | 1508±2338 | −291±1717 | −444 (−843 to −45) | <0.001 |
| WHO functional class§ | 87 | 0 patients in class I, 25 (29%) in class II, 60 (69%) in class III, 2 (2%) in class IV | 13 patients (15%) moved to lower class (indicating improvement), 68 (78%) stayed in same class, 6 (7%) moved to higher class | 173 | 3 patients (2%) in class I, 55 (32%) in class II, 107 (62%) in class III, 8 (5%) in class IV | 57 patients (33%) moved to lower class (indicating improvement), 107 (62%) stayed in same class, 9 (5%) moved to higher class | — | 0.003 |
| Borg dyspnea score¶ | 88 | 4±2 | 0.2±2.4 | 173 | 4±2 | −0.8±2 | — | 0.004‖ |
| EQ-5D score** | 87 | 0.66±0.25 | −0.08±0.34 | 172 | 0.64±0.24 | 0.06±0.28 | 0.13 (0.06 to 0.21) | <0.001‖ |
| LPH score†† | 86 | 46±23 | −2±19 | 170 | 41±22 | −7±19 | −6 (−10 to −1) | 0.1‖ |
| **Hemodynamic variables‡‡** | | | | | | | | |
| Pulmonary-artery pressure (mm Hg) | 84 | 44±10 | 0.8±7.3 | 156 | 45±13 | −4±7 | −5 (−7 to −3) | <0.001 |
| Mean arterial pressure (mm Hg) | 78 | 95±11 | −0.3±11.8 | 155 | 95±12 | −9±12 | −9 (−12 to −6) | <0.001 |
| Right atrial pressure (mm Hg) | 84 | 9±6 | −0.6±5.2 | 157 | 9±5 | −1±5 | −0.6 (−1.7 to 0.6) | 0.4 |
| Cardiac output (liters/min) | 83 | 4±1 | −0.03±1.07 | 155 | 4±1 | 0.8±1.1 | 0.9 (0.6 to 1.1) | <0.001 |
| Pulmonary-capillary wedge pressure (mm Hg) | 83 | 9±4 | 0.2±4.3 | 151 | 9±3 | 0.6±3.7 | 0.6 (−0.4 to 1.5) | 0.2 |
| Arterial oxygen saturation (%) | 87§§ | 94±2 | −3±8 | 172¶¶ | 94±3 | −2±4 | — | — |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Heart rate (beats/min) | 88 | 76±12 | 2±12 | 173 | 78±12 | 1±12 | — | — |
| $Pao_2$ (mm Hg) | 87‖‖ | 69±11 | −5±12 | 172¶¶ | 70±12 | −3±15 | — | — |

* Plus–minus values are means ±SD. The changes from baseline to the end of week 16 are arithmetic means. The least-squares mean difference was calculated by analysis of covariance for the change from baseline to the last visit. NT-proBNP denotes N-terminal pro–brain natriuretic peptide, and $Pao_2$ partial pressure of arterial oxygen.

† P values were calculated with use of the stratified Wilcoxon test for the change from baseline to the last visit.

‡ The primary end point was analyzed in the modified intention-to-treat population as the change from baseline to the last observed value (not including follow-up) among patients who completed the study or withdrew; the worst value (0 m) was imputed in the case of death or clinical worsening without a termination visit or without a measurement at the termination visit.

§ The change in the WHO functional class was analyzed with the use of a stratified Wilcoxon test.

¶ The Borg dyspnea scale ranges from 0 to 10, with 0 representing no dyspnea and 10 maximal dyspnea. The change in the Borg dyspnea score was analyzed with the use of a stratified Wilcoxon test; an analysis of covariance was not specified for this variable owing to the nonnormal distribution of the data.

‖ These analyses were only exploratory, owing to the hierarchical testing procedure.

** Scores on the EuroQol Group 5-Dimension Self-Report Questionnaire (EQ-5D) range from −0.6 to 1.0, with higher scores indicating a better quality of life.

†† Scores on the Living with Pulmonary Hypertension (LPH) questionnaire (an adaptation of the Minnesota Living with Heart Failure Questionnaire) range from 0 to 105, with higher scores indicating worse quality of life.

‡‡ All the analyses of hemodynamic variables were exploratory analyses, with the exception of heart rate, which was analyzed descriptively (and therefore has no P value associated with it).

§§ Data at week 16 were missing for 7 patients.

¶¶ Data at week 16 were missing for 20 patients.

‖‖ Data at week 16 were missing for 6 patients.

effect was consistent across predefined patient subgroups (Fig. S2 and Table S3 in the Supplementary Appendix).

### SECONDARY END POINTS

Pulmonary vascular resistance decreased by 226 dyn · sec · $cm^{-5}$ in the riociguat group, as compared with an increase of 23 dyn · sec · $cm^{-5}$ in the placebo group (least-squares mean difference, −246 dyn · sec · $cm^{-5}$; 95% CI, −303 to −190; P<0.001) (Table 2). Riociguat was also associated with significant improvement in other hemodynamic variables, including mean pulmonary-artery pressure and cardiac output (Table 2). Levels of NT-proBNP were significantly reduced in patients treated with riociguat, and changes in WHO functional class at 16 weeks also significantly favored riociguat (Table 2).

There was no significant difference in the incidence of clinical-worsening events between the riociguat and placebo groups (2% and 6%, respectively; P=0.17) (Table 3). The Kaplan–Meier estimates of the proportion of patients with clinical worsening are provided in Figure S3 in the Supplementary Appendix.

On the basis of the prespecified hierarchical testing procedure, analyses of the Borg dyspnea score and quality-of-life data were considered exploratory (Table S4 in the Supplementary Appendix). The Borg dyspnea score decreased by 0.8 points in the riociguat group and increased by 0.2 points in the placebo group (P=0.004). There was a nominally significant difference between the two groups in the change in the EQ-5D score but not in the change in the LPH questionnaire score (Table 2).

### SAFETY

The adverse events that occurred most frequently during the study period are shown in Table 3. The most frequently occurring serious adverse events were right ventricular failure (in 3% of patients in each group), syncope (in 2% of the riociguat group and 3% of the placebo group), and hemoptysis (in 2% of the riociguat group). Drug-related serious adverse events in the riociguat group included syncope in three patients (2%) and gastritis, acute renal failure, and hypotension in one patient each (1%); in the placebo group, syncope and trauma occurred in one patient each (1%).

Five patients (3%) in the riociguat group and two (2%) in the placebo group discontinued the

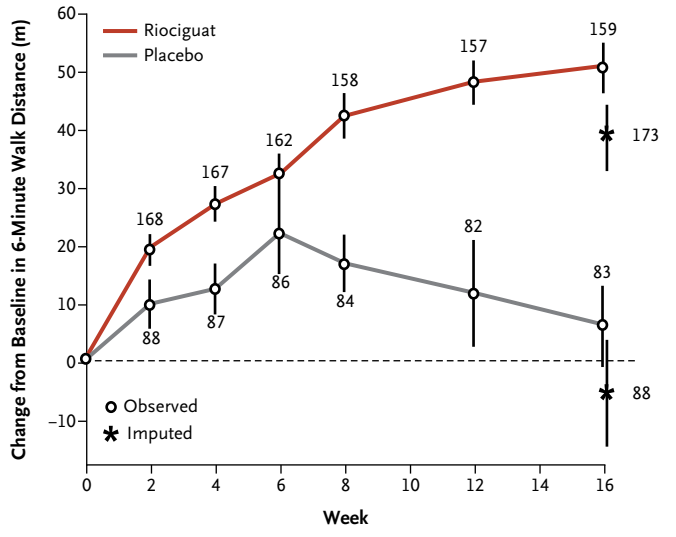


**Figure 2. Mean Change from Baseline in the 6-Minute Walk Distance.**

Mean (±SE) changes from baseline in the distance walked in 6 minutes during the 16-week study are shown in the modified intention-to-treat population without imputation of missing values, with the imputed values also provided at week 16. The number at each data point indicates the number of patients included in the assessment at that time point. The least-squares mean difference in the distances at week 16 was 46 m (95% CI, 25 to 67; P<0.001). The last observed value (not including follow-up) was carried forward for patients who completed the study or withdrew; the worst value (0 m) was imputed in the case of death or clinical worsening without a termination visit or without a measurement at the termination visit.

study drug owing to adverse events. For one patient in the riociguat group, the adverse events (diarrhea, heartburn, nausea, vomiting, and headache) leading to discontinuation were considered by the investigator to be related to the study drug. Four patients (2%) in the riociguat group and two (2%) in the placebo group discontinued the study drug owing to serious adverse events. In the riociguat group, these events included right heart decompensation, vaginal bleeding, overdose of study drug (attempted suicide), and worsening of general condition; in the placebo group, the events included right heart failure and cardiocirculatory arrest. None of these serious adverse events were considered to be related to the study drug. Deaths related to adverse events occurred in two patients (1%) in the riociguat group (one each with heart failure and acute renal failure) and in three patients (3%) in the placebo group (one each with respiratory insufficiency, circulatory arrest, and cardiac arrest). The case of acute renal failure was considered by the investigator to be related to the study drug.

### LONG-TERM EXTENSION STUDY

A total of 237 patients (98% of the patients who completed the study) entered the long-term extension study, CHEST-2, in which study assignments were concealed for the first 8 weeks and treatment was open-label thereafter. Of these patients, 194 (129 patients from the riociguat group and 65 from the placebo group in CHEST-1) were included in an interim analysis in CHEST-2 that included data collected up to May 2012, and 182 (94%) were still participating in the study after a median treatment duration of 336 days. An exploratory analysis of the first 12 weeks of CHEST-2 showed further increases in the 6-minute walk distance in the group that received riociguat in CHEST-1. A mean (±SD) increase of 63±64 m over the baseline distance in CHEST-1 for the 129 patients in this group was observed at week 12 of CHEST-2. The same group had an increase of 51±62 m at week 16 of CHEST-1.

## DISCUSSION

In this trial, riociguat, a soluble guanylate cyclase stimulator, significantly improved exercise capacity in patients with chronic thromboembolic pulmonary hypertension who were deemed to be ineligible for surgery or who had persistent or recurrent pulmonary hypertension after undergoing pulmonary endarterectomy. Significant improvements were also observed in the clinically relevant secondary end points, including pulmonary vascular resistance, NT-proBNP level, and WHO functional class.

Pulmonary endarterectomy, the only treatment option currently recommended for patients with chronic thromboembolic pulmonary hypertension, improves hemodynamics, exercise capacity, and survival.[16-18] These patients should always be assessed for operability at an experienced center.[6,9] However, only approximately 63% of patients are eligible for surgery,[5] and the disorder persists or recurs after surgery in 5 to 35% of patients.[16,19-21]

Hemodynamic measurements, an important end point in studies of pulmonary hypertension, provide a robust and objective measure of the status of the pulmonary circulation and are predictive of the outcome. For example, when baseline pulmonary vascular resistance exceeds 900 dyn·sec·cm$^{-5}$, mortality has been shown to increase.[22] Reductions in pulmonary vascular resistance have been asso-

ciated with improved outcomes of medical treatment for pulmonary arterial hypertension[23,24] and increased survival after surgery among patients with chronic thromboembolic pulmonary hypertension.[25]

The magnitude of the decrease in pulmonary vascular resistance with riociguat that we observed in this study appears to be clinically relevant, on the basis of the results of previous studies of therapies for pulmonary hypertension.[26,27] It has also been shown that high preoperative levels of pulmonary vascular resistance increase the risk of death during surgery among patients with chronic thromboembolic pulmonary hypertension,[25] and a reduction in pulmonary vascular resistance before surgery may improve the postoperative course.[28] Future studies with riociguat could address its usefulness in reducing preoperative hemodynamics and improving physical condition in patients who are eligible for pulmonary endarterectomy.[15]

The current study also showed a benefit of riociguat with respect to WHO functional class. In addition to its direct relevance to patients' perception of a treatment benefit, improvement in functional class correlates with survival among patients with chronic thromboembolic pulmonary hypertension and those with pulmonary arterial hypertension.[24,29,30]

The only other drug that has been evaluated for chronic thromboembolic pulmonary hypertension in a randomized, controlled study is the endothelin-receptor antagonist bosentan. In the 16-week Bosentan Effects in Inoperable Forms of Chronic Thromboembolic Pulmonary Hypertension (BENEFIT) study, bosentan significantly decreased pulmonary vascular resistance, as compared with placebo (treatment effect, –24.1%), but not the 6-minute walk distance (mean difference, 2.2 m).[26] Although direct comparisons of the results of different clinical trials require caution, in the current study, riociguat significantly improved both hemodynamics and exercise capacity, as compared with placebo, and the magnitude of the change in pulmonary vascular resistance was greater than that observed with bosentan. Moreover, riociguat was associated with robust improvement in the 6-minute walk distance both in patients who were ineligible for surgery and in those with persistent or recurrent pulmonary hypertension after pulmonary endarterectomy (increases of 54 m and 26 m, respectively).

**Table 3. Clinical Worsening and Adverse Events.***

| Event | Placebo (N=88) | Riociguat (N=173) |
|---|---|---|
| | *number of patients (percent)* | |
| Clinical worsening | | |
| All events | 5 (6) | 4 (2)† |
| Hospitalization due to pulmonary hypertension | 1 (1) | 0 |
| Start of new treatment for pulmonary hypertension | 1 (1) | 2 (1) |
| Decrease in 6-min walk distance due to pulmonary hypertension | 2 (2) | 1 (1) |
| Persistent worsening of WHO functional class due to pulmonary hypertension | 1 (1) | 0 |
| Death | 3 (3) | 2 (1) |
| Adverse events | | |
| Any | 76 (86) | 159 (92) |
| Headache | 12 (14) | 43 (25) |
| Dizziness | 11 (12) | 39 (23) |
| Dyspepsia | 7 (8) | 31 (18) |
| Peripheral edema | 18 (20) | 27 (16) |
| Nasopharyngitis | 8 (9) | 26 (15) |
| Nausea | 7 (8) | 19 (11) |
| Vomiting | 3 (3) | 17 (10) |
| Diarrhea | 4 (5) | 17 (10) |
| Hypotension | 3 (3) | 16 (9)‡ |
| Upper respiratory tract infection | 4 (5) | 10 (6) |
| Increase in international normalized ratio | 4 (5) | 10 (6) |
| Constipation | 1 (1) | 10 (6) |
| Prolonged activated partial-thromboplastin time | 2 (2) | 8 (5) |
| Cough | 16 (18) | 9 (5) |
| Chest pain | 4 (5) | 7 (4) |
| Dyspnea | 12 (14) | 8 (5) |
| Back pain | 5 (6) | 7 (4) |
| Increase in serum creatinine level | 5 (6) | 3 (2) |
| Pain in extremity | 5 (6) | 3 (2) |
| Insomnia | 6 (7) | 4 (2) |
| Syncope | 3 (3) | 4 (2) |

* The adverse events listed are those that occurred in at least 5% of the patients in either group during the treatment period or up to 2 days after the end of treatment. The incidence of syncope as an adverse event of special interest is also reported.

† P=0.17 as compared with placebo, with the use of a stratified log-rank test.

‡ Of the 16 cases of hypotension reported in the riociguat group, 8 were reported as mild and 8 as moderate.

This may suggest that the nitric oxide–soluble guanylate cyclase–cyclic guanosine monophosphate pathway has a role in the pathologic features underlying chronic thromboembolic pulmonary hypertension, including impairments in nitric oxide–mediated production of endogenous cyclic guanosine monophosphate and in progressive remodeling of the remaining perfused areas of the pulmonary vascular bed.[2,31]

An obvious limitation of CHEST-1 was the lack of follow-up efficacy measurements in patients who withdrew from the study. However, sensitivity analyses that used a variety of approaches to impute missing data suggest that the results are reliable, despite these losses to follow-up.

In conclusion, riociguat significantly improved the 6-minute walk distance, pulmonary vascular resistance, and other clinical outcomes in patients with chronic thromboembolic pulmonary hypertension who were deemed to be ineligible for surgery or who had persistent or recurrent pulmonary hypertension after undergoing pulmonary endarterectomy.

Supported by Bayer HealthCare.

Dr. Ghofrani reports serving as a board member for Actelion Pharmaceuticals, Bayer, GlaxoSmithKline, Merck, Novartis, Pfizer, and Takeda Pharmaceuticals; receiving consulting fees from Actelion Pharmaceuticals, Bayer HealthCare, GlaxoSmithKline, Eli Lilly, Merck, Novartis, Pfizer, and Takeda Pharmaceuticals; receiving lecture fees from Actelion Pharmaceuticals, Bayer HealthCare, GlaxoSmithKline, Eli Lilly, Novartis, and Pfizer; and receiving grant support through his institution from Actelion Pharmaceuticals, Bayer HealthCare, Novartis, and Pfizer. Dr. D'Armini reports receiving consulting fees from Bayer HealthCare and lecture fees from Actelion Pharmaceuticals, Bayer HealthCare, and Pfizer. Dr. Grimminger reports serving as a board member for Bayer HealthCare and Pfizer; receiving consulting fees from Actelion Pharmaceuticals, Bayer HealthCare, and Pfizer; receiving lecture fees from Actelion Pharmaceuticals, Bayer HealthCare, Eli Lilly, Novartis, and Pfizer; and receiving grant support through his institution from Bayer HealthCare and Pfizer. Dr. Hoeper reports serving as a board member for and receiving consulting and lecture fees from Actelion Pharmaceuticals, Bayer HealthCare, GlaxoSmithKline, Novartis, Pfizer, and Eli Lilly; and receiving payment for the development of educational presentations from Pfizer. Dr. Jansa reports receiving consulting and lecture fees from Actelion Pharmaceuticals, Bayer HealthCare, AOP Orphan, United Therapeutics, and GlaxoSmithKline; and receiving grant support from Actelion Pharmaceuticals and United Therapeutics. Dr. Kim reports receiving consulting fees from Bayer HealthCare. Dr. Mayer reports receiving lecture fees from Actelion Pharmaceuticals, Bayer HealthCare, GlaxoSmithKline, and Pfizer. Dr. Simonneau reports serving as a board member for and receiving travel support from Actelion Pharmaceuticals, Bayer HealthCare, GlaxoSmithKline, Novartis, Eli Lilly, and Pfizer; receiving consulting and lecture fees from Actelion Pharmaceuticals, Bayer HealthCare, GlaxoSmithKline, Eli Lilly, and Pfizer; and receiving grant support through his institution from Actelion Pharmaceuticals, Bayer HealthCare, GlaxoSmithKline, Eli Lilly, and Pfizer. Dr. Wilkins reports receiving consulting and lecture fees from Pfizer and Novartis. Drs. Fritsch, Neuser, and Weimann report being employees of Bayer HealthCare. Dr. Fritsch reports holding stock in Bayer HealthCare, and Dr. Weimann reports holding five riociguat patents, through Bayer HealthCare, for indications other than chronic thromboembolic pulmonary hypertension. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank Mike Kenward, Ph.D., from the London School of Hygiene and Tropical Medicine for advice on the missing-data sensitivity analysis.

## APPENDIX

The authors' affiliations are as follows: the University of Giessen and Marburg Lung Center, Giessen, member of the German Center for Lung Research (H.-A.G., F.G.), Clinic for Respiratory Medicine, Hannover Medical School, Hannover (M.M.H.), Kerckhoff Heart and Lung Center, Bad Nauheim (E.M.), and Global Clinical Development, Bayer HealthCare, Wuppertal (A.F., D.N., G.W.) — all in Germany; Department of Medicine (H.-A.G.) and National Institute for Health Research and Wellcome Trust Imperial Centre for Translational and Experimental Medicine (M.R.W.), Imperial College London, and Hammersmith Hospital (M.R.W.) — both in London; Division of Cardiac Surgery, Istituto di Recovero e Cura a Carattere Scientifico Policlinico San Matteo, University of Pavia School of Medicine, Pavia, Italy (A.M.D.); Clinical Department of Cardiology and Angiology of the First Faculty of Medicine and General Teaching Hospital, Prague, Czech Republic (P.J.); Division of Pulmonary and Critical Care Medicine, School of Medicine, University of California, San Diego, San Diego (N.H.K.); Assistance Publique–Hôpitaux de Paris, Service de Pneumologie, Hôpital Bicêtre, Université Paris-Sud, Laboratoire d'Excellence en Recherche sur le Médicament et Innovation Thérapeutique, and INSERM Unité 999, Le Kremlin–Bicêtre, France (G.S.); and Beijing Institute of Respiratory Medicine, Beijing Chao Yang Hospital, Department of Respiratory Medicine, Capital Medical University, Beijing Key Laboratory of Respiratory and Pulmonary Circulation Disorders, Beijing (C.W.).

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